

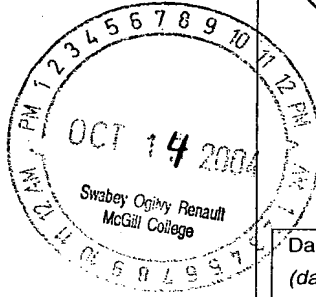
PATENT COOPERATION TREATY

Rec'd PCT/PTO 20 DEC 2004

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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Montreal, Québec H3A 2Y3
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PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing
(day/month/year)

06.10.2004

Applicant's or agent's file reference

~~15890-1PCT~~ 6013-149 PCT MG

IMPORTANT NOTIFICATION

International application No.

PCT/CA 03/00939

International filing date (day/month/year)

20.06.2003

Priority date (day/month/year)

05.07.2002

Applicant

UNIVERSITE LAVAL et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international
preliminary examining authority:



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INTERNATIONAL PRELIMINARY EXAMINATION REPORT (PCT Article 36 and Rule 70)

Applicant's or agent's file reference 15890-1PCT		FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/416)
International application No. PCT/CA 03/00939	International filing date (day/month/year) 20.06.2003	Priority date (day/month/year) 05.07.2002
International Patent Classification (IPC) or both national classification and IPC A61K45/00		
Applicant UNIVERSITE LAVAL et al.		



- This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
- This REPORT consists of a total of 8 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 27.01.2004	Date of completion of this report 06.10.2004
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Böhmerova, E Telephone No. +49 89 2399-7859 <div style="text-align: right;">  </div>

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/CA 03/00939**

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, Pages

1-35 as originally filed

Claims, Numbers

1-13 as originally filed

Drawings, Sheets

1/12-12/12 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

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5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-11

because:

☒ the said international application, or the said claims Nos. 1-11 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	-
	No: Claims	1,12,13
Inventive step (IS)	Yes: Claims	-
	No: Claims	1,12,13
Industrial applicability (IA)	Yes: Claims	12,13
	No: Claims	-

2. Citations and explanations

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see separate sheet

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Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Independent claim 1 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Cited documents

Reference is made to the following documents:

- D1: US-A-5 731 166 (GECZY CAROLYN ET AL) 24 March 1998
- D2: US-A-6 103 497 (CORLEY NEIL C ET AL) 15 August 2000
- D3: EP-A-0 263 072 (CIBA GEIGY AG) 6 April 1988
- D4: DUNN C J ET AL: 'Increased expression of neutrophil MRP8 and MRP14 is associated with vascular adhesion molecule activation and differential leukocyte infiltration in delayed-type hypersensitivity suggesting a proinflammatory role for S100 calcium-binding proteins' DATABASE BIOSIS, Acc. No. PREV199799379823
- D5: YEN TINA ET AL: 'Induction of the S100 chemotactic protein, CP-10, in murine microvascular endothelial cells by proinflammatory stimuli', BLOOD, vol. 90, no. 12, 15 December 1997, pages 4812-4821
- D6: LAGASSE E ET AL: 'MOUSE MRP8 AND MRP14, TWO INTRACELLULAR CALCIUM-BINDING PROTEINS ASSOCIATED WITH THE DEVELOPMENT OF THE MYELOID LINEAGE', BLOOD, vol. 79, 1992, pages 1907-1915
- D7: LACKMANN M: 'IDENTIFICATION OF A CHEMOTACTIC DOMAIN OF THE PRO-INFLAMMATORY S100 PROTEIN CP-10' JOURNAL OF IMMUNOLOGY, vol. 150, no. 7, 1 April 1993, pages 2981-2991
- D8: DEVERY JANNINE M ET AL: 'Acute inflammatory activity of the S100 protein CP-10: Activation of neutrophils in vivo and in vitro.' JOURNAL OF IMMUNOLOGY, vol. 152, no. 4, 1994, pages 1888-1897
- D9: ROULEAU PASCAL ET AL: 'The calcium-binding protein S100A12 induces

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neutrophil adhesion, migration, and release from bone marrow in mouse at concentrations similar to those found in human inflammatory arthritis.' CLINICAL IMMUNOLOGY, vol. 107, no. 1, 20 April 2003, pages 46-54

Unless indicated otherwise reference is made to the passages considered relevant in the search report.

Novelty

Subject-matter of independent claims 1, 12, 13 is considered to lack novelty under Art. 33(1) and (2) PCT for the following reasons:

Present claims 1 and 13 are directed to a method for systemic modulation of an inflammatory reaction in an individual comprising administering a chemotactic factor inhibitor selected from the group consisting of an S100 protein, a protein of MRP family, calprotectin and calgranulin and the analogical second medical use. Claim 12 is directed to a composition for modulating an inflammatory reaction comprising a chemotactic factor inhibitor selected from the group consisting of an S100 protein, a protein of MRP family, calprotectin and calgranulin.

D1 discloses CP-10 polypeptide, a pharmaceutical composition comprising such polypeptide and a method for modulating an inflammatory response in a mammal comprising the step of administering CP-10 protein. CP-10 is murine S100A8 (see D9). D1 further teaches the use of monoclonal antibodies against CP-10 or non-functional analogues or antagonist of CP-10 for inhibition of inflammation in the treatment of conditions such as rheumatoid arthritis, systemic lupus erythematosus, coeliac disease, multiple sclerosis, rejecting grafts, tumors etc..

D2 discloses S100P proteins S100P1 and S100P2, pharmaceutical compositions comprising S100P1 or S100P2 (column 3, lines 14-17, column 4, lines 19-22) and the use of these compositions for the diagnosis, prevention or treatment of neuronal, vesicle trafficking, immunological and neoplastic disorders (column 11, lines 1-7). D2 further teaches the use of antagonists or antibodies against S100P protein in the treatment or prevention of diseases including inflammatory bowel disease, rheumatoid arthritis, osteoarthritis, leukemia etc..

The above disclosure of D1 and D2 anticipates novelty of present claims 1, 12 and 13.

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Inventiveness

As the subject-matter of claims 1, 12, 13 is considered as lacking novelty, no inventiveness can be acknowledged at this stage.

In case novelty of present claims 1, 12 and 13 is acknowledged, the subject-matter of those claims would be considered as lacking an inventive step under Article 33(1) and (3) PCT for the following reasons:

The problem to be solved by the application can be defined as to provide a medicament for modulation of inflammatory reaction. Solution proposed by the application is an inhibitor of a chemotactic factor selected from S100 protein, a protein of MRP family, calprotectin or calgranulin. The application does not comprise experimental data directly proving such an effect of chemotactic factor inhibitors. The data present in the application prove the following facts:

- injection of LPS into air pouch (model of inflammation) causes accumulation of leukocytes, release of S100A8, S100A9 and S100A8/A9 in the place of injection and increase of circulating neutrophils and S100A9 and S100A8/A9 levels;
- these effects are inhibited by anti-S100A8 or anti-S100A9 antibodies;
- intravenous injection of S100A8 or S100A9 causes serum neutrophilia and release of bone marrow neutrophils into blood.

However, all the above effects are known from the prior art - see documents D3-D8. D3 teaches that serum levels of MRP-8 and/or MRP-14 are elevated in inflammatory conditions.

D4 teaches that infiltrating neutrophils express and release MRP8 and MRP14. This may represent an important systemic and local mechanism for recruitment of neutrophils and monocytes into the delayed type hypersensitivity inflammatory site through bone marrow mobilization and chemotaxis of neutrophils and monocytes.

D5 teaches that CP-10 (murine S100A8) is expressed in neutrophils, LPS-activated macrophages and LPS-activated murine endothelioma cell lines.

D6 discloses that MRP8 and MRP14 are highly expressed in recruited neutrophils and monocytes in thoglycollate-induced peritoneal inflammatory exudates.

D7 teaches that intradermal injection of native CP-10 elicited sustained recruitment of neutrophils and mononuclear cells over 24 hours in rats. Sustained cellular recruitment is typical for a delayed type hypersensitivity responses.

D8 teaches that CP-10 has a potent chemotactic activity for murine and human myeloid

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cells. An i.p. injection of CP-10 induced infiltration of neutrophils in mice. LPS injection to murine footpads induced inflammation and secretion of CP-10.

If the experimental data provided by the application should be considered to be sufficient to prove that the claimed solution actually solves the technical problem, this solution must be directly derivable from those data without any further inventive activity. If this applies, the same conclusion must apply to the analogical data known from the prior art (D3-D8). Therefore, those data should be considered as being sufficient to lead a skilled person to the claimed solution without involvement of an inventive activity. Consequently, the solution as claimed is to be considered as being obvious based on the data known from D3-D8.

Industrial applicability

Subject-matter of independent claims 12, 13 is considered to be industrially applicable under Art. 33(1) and (4) PCT.

For the assessment of the independent claim 1 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.